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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/262,126	03/03/1999	BRIAN S. MILLER	GC396-2	8961

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GENENCOR INTERNATIONAL, INC.
ATTENTION: LEGAL DEPARTMENT
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PALO ALTO, CA 94304

EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/262,126	MILLER ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-10,12,14,15,27-40 and 52-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-10,12,14-15,27-40, 52-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 5-10, 12, 14-15, 27-40, 52-66 are currently pending in this application.

Applicants' arguments filed on 6-7-06, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-10, 14-15, 27-40, 52-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deweer et al. (US 6,074, 854 filed 12-23-97, issued 6-13-2000) and McPherson et al. (Biochemical Soc. Trans., 1988, vol. 16(5): 723-724) or Albertson (Biochim. Biophys. Acta, Vol. 1354:35-39, 1997).

This rejection is based on printed publications and a patent. Claims 5-10, 14-15, 27-40, 52-66 in this instant application are drawn to a modified pullulanase from *B.deramificans* T89.117D with an amino acid sequence of SEQ ID NO: 2, wherein the modification is a deletion of about 98, 100, 102, 200 amino acids from the amino terminus, wherein the modified pullulanase is produced by culturing a host cell comprising a nucleic acid which is at least 90% identical to SEQ ID NO: 1 encoding a truncated pullulanase wherein the host cell is *B.licheniformis* in which certain proteases are inactivated or eliminated. The claims are also

drawn to compositions comprising the above-modified pullulanase and compositions further comprising additional enzymes such as glucoamylase isolated from *Aspergillus* strains and wherein the modified pullulanase is 60 or 80% of the composition and wherein the composition is in the solid or liquid form.

Deweer et al. teach a pullulanase obtained from a Gram-positive bacteria such as *B.deramificans* T89.117D produced by a method of culturing a host cell such as *B.licheniformis* in which certain protease genes have been inactivated. The reference also teaches the method of making the recombinant enzyme by obtaining the host cell transformed with a polynucleotide having more than 90% identity to SEQ ID NO:1 (see sequence alignment sent in the previous office action). The reference teaches the compositions either in the solid form or liquid form comprising pullulanase wherein it is of the order of 60% of the total enzyme concentration. The reference also teaches compositions comprising additional enzymes such as glucoamylase isolated from *Aspergillus* strains (see claims in the reference). However, the reference does not teach modification of pullulanase by way of deletion of about 100, 200 or 300 N-terminal amino acids.

McPherson et al. teach that pullulanases are significantly large enzymes when compared to other polysaccharide hydrolases and that this large size reduces the efficiency with which it can function by restricting access to internal alpha 1,6 bonds within highly branched substrates. The reference teaches that proteolytic digestion and computer-based sequence analyses are being used in the art to define a functional "core" pullulanase. The reference provides sources for such computer based homology searches. As an example the reference provides a schematic illustration of the relative position of the 5 conserved "amylase" regions within a selection of

hydrolases in comparison to the large *K.pneumoniae* pullulanase. The reference teaches that the long N-terminal region lacks any polysaccharide binding or catalyzing sites. McPherson et al. teach the modification of deleting nearly 170 amino acid residues from the amino terminal end, which leads to approximately 30% higher activity than that of the native enzyme.

Albertson et al. also teach the modification of a pullulanase (from *C.saccharolyticus*), wherein nearly 381 nucleotides from the 5' region of the cDNA encoding a pullulanase was deleted resulting in a N-terminal truncated pullulanase. The reference also teaches that the deleted amino acid sequence is not essential for either activity or thermostability.

While both McPherson et al. and Albertson et al. do not teach a pullulanase isolated from a *Bacillus*, it appears that experiments involving truncation of N-terminal amino acids in pullulanase enzymes was well known in the art. These experiments appear to have been performed to determine the nature and the location of secretion signal, activity, catalytic site, transport across membrane and secretion into liquid medium.

It would have been obvious to one skilled in the art at the time the invention was made to combine the teachings of Deweer et al. with that of McPherson et al. and Albertson et al. to compare the large pullulanase provided by Deweer et al. with other *Bacillus* pullulanase just as taught by McPherson et al., followed by a method to make a modified pullulanase in which any number of amino acids up to at least a maximum of 381 amino acids from the N-terminal amino acids have been deleted. This is because Deweer et al. teach a pullulanase isolated from a Bacillus, *B.deramificans*, which is a very large size enzyme with more than 900 amino acids. McPherson et al. teach a method of increasing the efficiency of large size pullulanase by determining and deleting non-essential amino acids in the N-terminal region. Albertson et al.

and McPherson et al. demonstrate that deletion of up to at least 170 and 381 amino acids in such large size pullulanases does not affect the activity of the enzyme negatively but on the other hand increases the efficiency of the enzyme by nearly 30%. It would also be obvious for one skilled in the art to eliminate or inactivate protease genes in the expression hosts, such as Carlsberg protease or endo Glu C protease as Deweer et al. teach such inactivation of proteases such that the heterologous protein is not digested by the endogenous proteases.

Based on the above teachings, one of ordinary skill in the art would be motivated to delete N-terminal amino acids just as McPherson et al. by comparing and determining that N-terminal regions of large pullulanase do not have any conserved sequences for either activity or binding to polysaccharide and cleavage of such non-essential sequences results in higher efficiency of the enzyme. Those of ordinary skill in the art would also be motivated by Albertson et al. teaching in which up to 381 N-terminal amino acids have been deleted. One of ordinary skill in the art would have a reasonable expectation of success since Deweer et al. provide the nucleic acid encoding the pullulanase from *B.deramificans* in a host cell such as *B. licheniformis* in which protease genes have been inactivated and also provide the compositions comprising up to 60% of pullulanase in order to perform the modification.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the above rejection, applicants have traversed arguing at length that the invention is not rendered obvious by the references. In addition applicants make an issue of several previous Office actions and the statement made by the examiner that the rejection is based on printed publications and a patent. Applicants also maintain that they have presented a

persuasive argument that the claims were not obvious in the response filed on July 28, 2003 and therefore they need only show why the cited publications and patent do not render the claimed invention obvious in light of these three documents as there has been no notice that any other evidence is being relied upon. The above arguments are not entirely clear to the Examiner. The significance of making an issue of the examiner's statement in the previous Office actions is also not clear to the Examiner.

In response to the above rejection, applicants continue to maintain that there is no teaching or suggestion to look for biologically active pullulanase fragments in Deweer et al. and there is nothing in Deweer et al. that would suggest to or motivate the skilled artisan to truncate the *Bacillus* pullulanase or to combine its teachings with McPherson et al. or Albertson et al.

With reference to McPherson et al. reference applicants submit that at best the reference teaches that there may be some length of the N-terminal region of pullulanase that has no defined catalytic function for the *Klebsiella* pullulanase and that there is no suggestion that the lack of defined catalytic function found in Klebsiella would be similarly found in an unrelated and non- homologous pullulanase. Applicants also argue that the reference is silent on whether or not other truncated pullulanases, in particular *Bacillus* pullulanases, would possess similar properties, characteristics or corresponding increases in activity. Applicants also argue that the combination of the Deweer et al. and McPherson et al. reference fails to suggest or motivate (page 12 of response) because the predicted amino acid sequences of pullulanases from *Klebsiella pnuemoniae* strains W70 and FG9 are very similar and provide the basis for the design of experiments to examine pullulanase function and therefore a similarity in the protein sequences was critical. Examiner respectfully disagrees with all the above arguments.

Applicants appear to be making a big deal on the minor points of the reference and try to focus away from the important information that the examiner has used from the references in order to reject the above claims. Contrary to applicant's argument, McPherson makes it very clear, the large structure of all the pullulanases and the existence of large stretches of amino acid sequences in the N-terminal that can be deleted without affecting the function of the enzyme. It is this kind of highly generalized information which could be used on any pullulanase, on which the examiner has based his rejection. McPherson et al. clearly state that pullulanases are significantly large enzymes when compared to other polysaccharide hydrolases and that this large size reduces the efficiency with which it can function by restricting access to internal alpha 1,6 bonds within highly branched substrates. The reference teaches that proteolytic digestion and computer-based sequence analyses are being used in the art to define a functional "core" pullulanase. The reference provides sources for such computer based homology searches. As an example the reference provides a schematic illustration of the relative position of the 5 conserved "amylase" regions within a selection of hydrolases in comparison to the large *K.pneumoniae* pullulanase. The reference limits its example to the *Klebsiella* enzyme and there is nothing in the reference, which would lead those skilled in the art to conclude that above teachings would not apply to pullulanases from other sources. Rather it is this kind of information that would be used by those skilled in the art in order to truncate pullulanases from other sources.

Applicants maintain a similar tangential argument with respect to the reference of Albertson et al. While examiner has used the above reference only to show that deletion of sequences in pullulanases appears to be well known in the art and practiced on pullulanases

from varied sources, applicants argue that there is no suggestion or motivation to delete sequences. Applicants also maintain that the combination fails to provide a reasonable expectation of success. Examiner respectfully disagrees. As stated earlier examiner has used the Albertson's reference to show that deletion of pullulanase is practiced to trim pullulanases from varied sources. The reference shows that there is a reasonable expectation of success in truncating any pullulanase from any source. Examiner has established from the above two references that one of skill in the art would doubt very little regarding the expectation of success in truncating the pullulanase.

Therefore, for all the above reasons, Examiner continues to maintain the above rejection of claims under 35 U.S.C. 103(a) as being *prima facie* obvious.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Deweer et al. (US 6,074, 854 filed 12-23-97, issued 6-13-2000). This rejection is based upon the public availability of a patent publication. Claim 12 of the instant application is drawn to a modified pullulanase isolated from *B.deramificans*, wherein the modification is an addition of at least has at least one amino acid added to the amino terminus of a mature pullulanase amino acid sequence, wherein the added amino acid is alanine. Deweer et al. teach the modification of an identical mature pullulanase by at least one amino acid, i.e., addition, substitution, deletion of at least one amino acid. However, the reference does not specifically teach that the added amino acid needs to be alanine.

However, with the above pullulanase in hand followed by the teaching of modifying it by at least one amino acid, it would have been obvious to those skilled in the art to modify the

enzyme of Deweer et al. by adding one amino acid anywhere in the sequence including the N-terminal and assay such modified enzymes of having the pullulanase activity. Since there are only twenty amino acids that can be used for modification, it would be obvious to those skilled in the art to use all or any of the twenty amino acids including alanine and select one or more of the modified enzyme that continues to have the activity. One of ordinary skill in the art would be motivated to do so in order to make a pullulanase that is simply different from that of an already patented enzyme in the art. One of ordinary skill in the art would have a reasonable expectation of success since there are only a limited number of amino acids that can be used for modification of an enzyme and Deweer et al. provide the mature pullulanase enzyme and also teach that a modification with at least one amino acid can be made along with techniques that can be used for making such modified enzyme.

Therefore, the above invention would have been *prima facie* obvious to those skilled in the art.

In response to the above rejection applicants argue that there is no teaching or suggestion in any of the cited references to specifically add an alanine to the N-terminus. Examiner respectfully disagrees with such an argument. First of all Examiner has used only the reference of Deweer et al. in this rejection. Furthermore, as stated in the rejection, the reference clearly teaches the modification of an identical mature pullulanase by at least one amino acid; i.e., addition, substitution, deletion of at least one amino acid. Examiner agrees that there is no teaching of specifically adding alanine. However, it would be obvious to one of ordinary skill in the art to add any one of the just twenty amino acid, alanine being one of them. Therefore the above rejection is maintained.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 5-10, 12, 14-15, 27-40, 52-66 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3 and 4 of U.S. Patent No.

6,074, 854 in view of McPherson et al. (Biochemical Soc. Trans., 1988, vol. 16(5) :723-724) or Albertson (Biochim. Biophys. Acta, Vol. 1354:35-39, 1997). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428,46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 5-10, 12, 14-15, 27-40, 52-66 of the instant application and claims 3-4 of the reference patent are both directed to pullulanases. While claims 3 and 4 of the patent are drawn to the pullulanase with SEQ ID NO:11/12, encoded by SEQ ID NO:10 and isolated from a *B.deramificans* strain, claims 5-10, 12, 14-15, 27-40, 52-66 of the instant application are also drawn to the very same enzyme but to truncated form of the same. Among all the different truncated forms of the pullulanase claimed in the instant application a good number of said truncated fragments are identical to one another. The portion of the specification (and the claims) in the reference patent that supports the enzyme includes several embodiments that would indeed anticipate or render obvious the truncated forms claimed in claims 5-10, 12, 14-15, 27-40, 52-66. Claims 5-10, 12, 14-15, 27-40, 52-66 cannot be considered patentably distinct over claims 3-4 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 3-4 of that patent and falls within the scope of claims 5-10, 12, 14-15, 27-40, 52-66 herein because combining the teachings of the patent with that of the teachings of either Albertson et al. or McPherson et al., it would have been obvious to one

having ordinary skill in the art to modify claims 3-4 of the reference by selecting a specifically disclosed embodiment that supports those claims i.e., a truncated form of the pullulanase. One of ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment when combined with the teachings in the art, i.e., the teachings of McPherson et al. and Albertson et al.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the above rejection, applicants make an issue of the Examiner's statement that "while claims 3 and 4 of the patent are drawn to the pullulanase with SEQ ID NO:11112, encoded by 8EQ ID NO:10 and isolated from a *B.deramificans* strain, claims 5-10, 12, 14-15, 27-40, 52,66 of the instant application are also drawn to the very same enzyme but to truncated form of the same" (Emphasis added) and argue that that this is a clear indication that there is a difference between the instant claims and the '854 claims. Examiner respectfully disagrees with such an argument to be persuasive to withdrawn the rejection. While there may be a difference between the claims of the patent and instant claims, the argument made in the rejection is that such difference would be obvious to one of ordinary skill in the art. This is because as stated earlier the '854 patent clearly teaches of the mutants, variants that can be made from the enzyme of that patent which includes deletion of at least one amino acid. Next, applicants also argue that Examiner fails to point to a disclosure in the '854 patent that provides support for the assertion that "the enzyme includes several embodiments that would indeed anticipate or render obvious the truncated forms claimed in claims 5-10, 12, 14, 15, 27-40, 52-66." See page 10, lines 15-18, of the December 29, 2005 Office Action and there is only the

nebulous reference "The portion of the specification (and the claims)" as support. Examiner respectfully disagrees with such an argument. There is no ambiguity regarding the support or the inclusion of the embodiments of instant claims in the patent of '854. As stated above, the '854 patent clearly embodies mutants, variants of the claimed pullulanases. The '854 patent makes it very clear that such variants include those arrived at by either adding, deleting or substituting at least one amino acid to the pullulanase sequence. Therefore contrary to applicant's argument examiner's assertion is correct and is free of any ambiguity. In view of all the above, the double patent rejection is maintained.

Conclusion

None of the claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

November 2, 2006